A COMPARATIVE STUDY & ANALYSIS OF OUTCOMES OF PAPSMEAR VERSUS LIQUID BASED CYTOLOGY WITH HISTOLOGY AS REFERENCE STANDARD IN CANCER CERVIX SCREENING

Dissertation Submitted for

M.D. OBSTETRICS AND GYNAECOLOGY
BRANCH - II

KILPAUK MEDICAL COLLEGE
Chennai.

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MEDICAL UNIVERSITY
CHENNAI
MARCH 2009

CERTIFICATE

This is to certify that this dissertation in **"A COMPARATIVE STUDY & ANALYSIS OF OUTCOMES OF PAPSMEAR VERSUS LIQUID BASED CYTOLOGY WITH HISTOLOGY AS REFERENCE STANDARD IN CANCER CERVIX SCREENING"** is a work done by **Dr.M.S.MANICKADEVI,** under my guidance during the period 2004 - 2007. This has been submitted in partial fulfillment of the award of M.D. Degree in Obstetrics and Gynaecology, (Branch -II) by the Tamil Nadu Dr.M.G.R. Medical University, Chennai - 600 032.

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ACKNOWLEDGEMENT

I sincerely thank **Prof.Dr.Thiagavalli Kirubakaran,** Dean Government Kilpauk Medical College for giving the permission to do this project.

I am greatly indebted to **Prof.Dr.Indirani Padmanabhan**, HOD for providing with the necessary facilities to carry out this study. Her continous support and guidance was of immense help to carry over with this project.

I thank **Dr.M.Muthulakshmi,M.D. DGO** and **Dr.T.A.Sridevi,M.D. D.G.O.** for guiding me to complete this desertation successfully.

I am greatly indebted to **Dr.A.Ezhilvizhi Alavandar, M.D.(Path) Ph.D.,** Professor Department of Pathology KMCH who showed constant interest in research and gave much of her valuable time providing cytology report and critical judgement.

I am very much thankful of **Dr.K.Vasanthi, M.D (Path)** for her support throughout the study.

My deepest thanks goes to the staff of Pathology Department who kindly contributed for the successful completion of this project.

I wish to thank my unit chiefs, Assistants and all my colleagues for their continuous support. My sincere thanks goes to Librarians for providing with relevant literature at all times.

I also thank **Mr.Padamanabhan,** ICMR for his statistical guidance for this study.

I also thank all the patients for their kind co-operation.

And most of all, I express my sincere gratitude to my family and my friends who helped me all the way through.

CONTENTS

INTRODUCTION

Cervical Cancer remains worldwide the second most common cancer among women accounting for 15% of all female cancers. It is the most common cancer among women in many developing countries constituting 20-30% of female cancers. In developed western countries it accounts for only 4 - 6% of female cancers. This difference largely reflects the impact of mass screening using cervical cytologic methods.

The purpose of cytologic screening is to identify those women who have a intraepithelial lesion (CIN) and not those who have cancer. If disease can be detected & treated at this preinvasive stage outcome should significantly improve.

For a screening system to be effective it must fulfill six basic requirements.

a) The test must detect the disease in a stage where early treatment will provide a Superior prognosis to treatment in a later stage.

b) The test must be sufficiently sensitive to detect the disease in an early stage.

c) The test must be sufficiently specific to distinguish non specific changes from the disease.

d) The test must be cost effective.

e) The test must be sufficiently simple to administer.

f) The screening procedure must be acceptable to those undergoing screening.

Cervical Cytology Meets All Of These Requirements

And also in all probability cervical cancer is the only gynecological malignancy that satisfies the well recognized WHO criteria for implementation of a screening program.

- Existence of well defined premalignant lesions
- Long Latent period in which premalignant change or occult cancers can be detected and effectively treated thereby altering the natural history of the disease.
- A clearly defined viral etiology, which could be incorporated as a marker in mass screening program.
- Easy & direct access of the uterine cervix for examination and sampling.
- Effective treatments available for the premaligant changes.

In the last 40 years developed countries like United States & British Columbia have shown a decrease in the incidence & mortality of invasive cancer cervix by effective cancer screening programmes. **(Coleman et al)**

But the scenario has not changed in the developing countries due to socioeconomic, cultural or political conditions. So the need to educate women & their health care providers about the importance of screening is evident.

AIM OF THE STUDY

1. To compare the cytologic diagnosis, specimen adequacy, sensitivity, cost effectiveness of Liquid based cytology with that of conventional pap test.

2. To correlate diagnostic colposcopy with histopathology in patients with abnormal cytology reports.

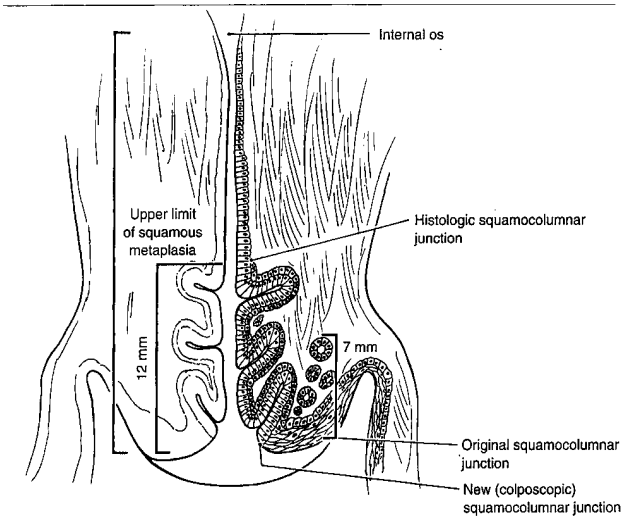
3. To study the accuracy of combined screening procedures.

REVIEW OF LITERATURE

The uterine cervix is the most common site of cancer in most developing countries including India. The age adjusted incidence of cancer of uterine cervix is **18.9/1,00,000** in Chennai. It is the 2nd most common cancer in female next to breast cancer in Chennai. **(population based cancer registry, ICMR, Adyar, Chennai 2003).**

Origin

The endocervical canal is lined by columnar epithelium and the portio vaginalis is lined by squamous epithelium and the place they meet is the squamo columnar junction. Normally there is not an abrupt transformation from columnar to squamous epithelium. A transitional area called “transformation zone” which consists of highly active young metaplastic cell is present. The transformation zone is highly active prior to birth, at menarche, during & after first pregnancy. The process of eversion exposes the columnar epithelium to the low vaginal PH which is the main trigger for metaplastic activity & the vaginal PH is under the influence of estrogen. The young metaplastic cells possess the property of phagocytosis. Early sexual activity which when occurs during this high metaplastic activity provides mutagens like sperms, virus and foreign bodies. The nucleicacids of sperms and virus may get incorporated in the cells during the process of active mitosis & get transformed to abnormal cells.



COLUMNAR EPITHELIUM

Low vaginal PH

Early metaplasia

Physiological Metaplasia

Normal transformation zone

Well differentiated squamous Epithelium

Some external factors act as mutagens

Atypical metaplasia

Abnormal transformation zone

Adequate Host response

No progression

Inadequate Host response

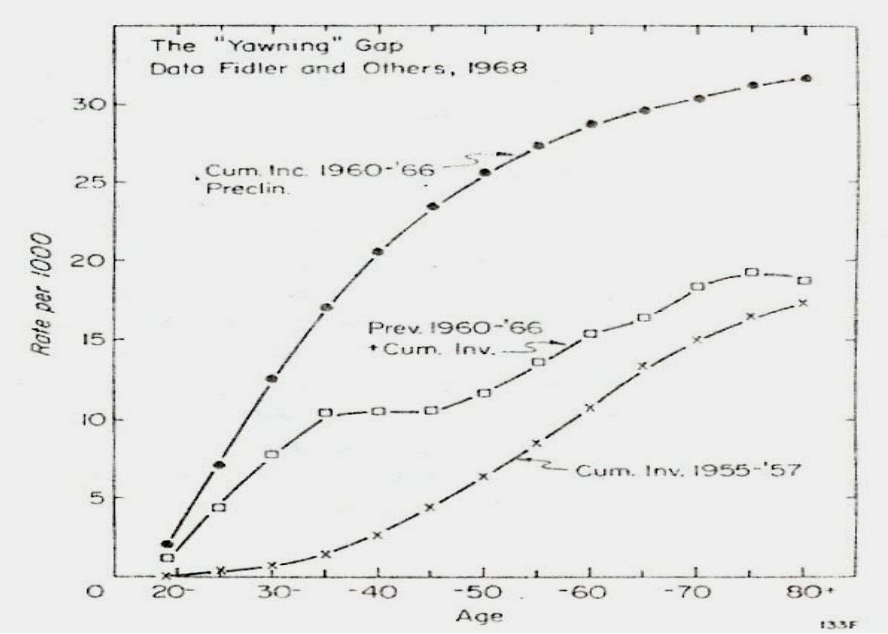
Dysplasia

CIS

Natural History

Squamous cell carcinoma of the cervix fulfills the model for a classic multistage disease beginning with the acquisition of a precursor lesion, morphologic progression of the precursor during the course of time, and in some cases, the development of invasive carcinoma. The fact that this process takes as much as 20 years to evolve has been the basis for cytologic screening for detection of preinvasive disease.

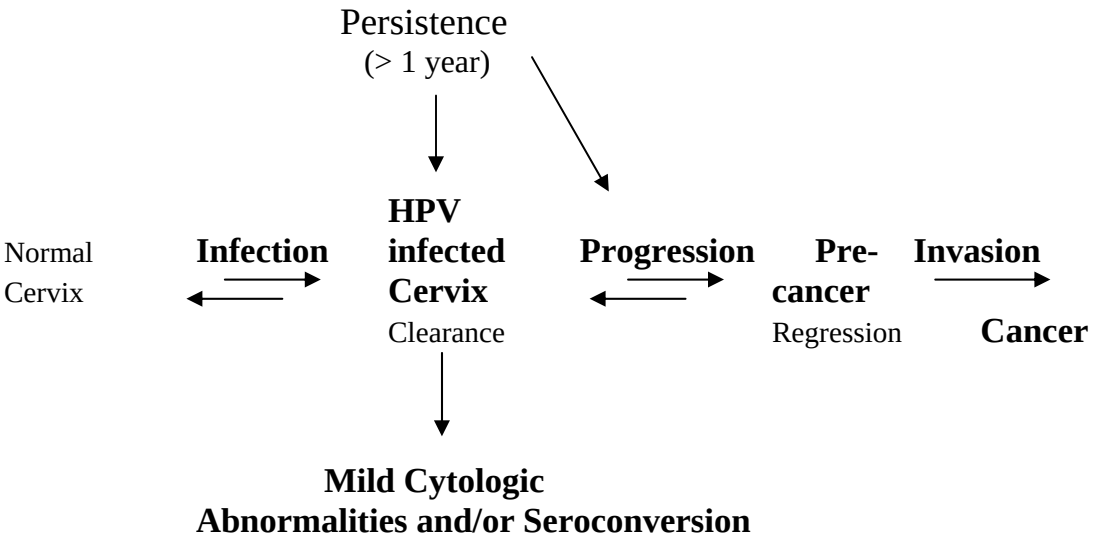
DUNN described the ***yawning gap*** phenomenon in 1968 of cancer cervix.



The graph shows substantial gap between cumulative incidence of insitu carcinoma and that of invasive carcinoma even when added to the later the prevalence of preclinical carcinoma.

Barron & Richart estimated that 66% would progress from cytological dysplasia to carcinoma insitu over a 10 year follow up.

Barron et al estimated that the duration of carcinoma insitu ranged from 3-10 years.



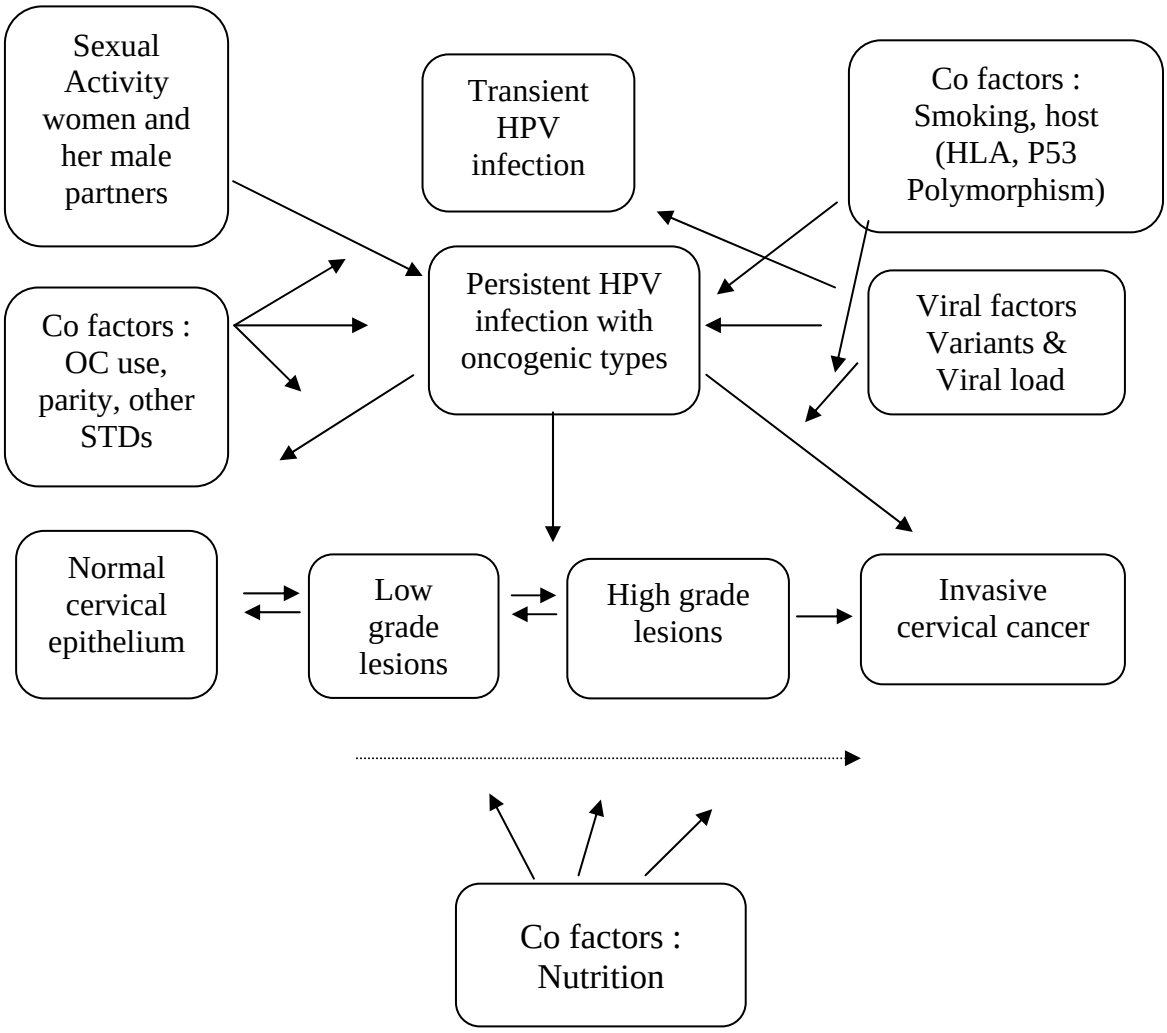
Natural History of CIN - Literature review - Ostor (1993)

	Patients	Regress	Persist	Progress to CIN 3	Progress to invasive cancer
CIN 1	4,504	57%	32%	11%	1%
CIN 2	2,247	43%	35%	22%	5%
CIN 3	767	32%	>56%	-	>12%

Epidemiology

The average age of patients with carcinoma insitu reproducibly is 10-15 years less than the average age of patients with invasive cancer of the cervix. Numerous studies of epidemiology of cervical cancer have shown strong associations with several risk factors.

A MULTIFACTORIAL MODEL OF CERVICAL CANCER ETIOLOGY



Historical Background of terminology

The proposal that invasive squamous carcinoma of the cervix arises through progression of a preinvasive lesion as apposed to a *de novo* event was initially postulated by **SCHAUENSTEIN in 1908.**

The term carcinoma in situ (CIS) was later introduced to describe cancerous changes confined to the epithelium.

The concept of cervical intrapitnelial neoplasia (CIN) was introduced by **Richart 1967.**

CIN is a histological term used to describe a full thickness epithelial change.

CIN is divided for convenience utility into three categories CIN 1,2,3.

Dyskaryosis literally mean *'Bad Kernel'* and identified by changes in the nuclear pattern. According to Bethesda classification,

Nuclear abnormality in mature cells represent LSIL

Nuclear abnormality in immature cells represent HSIL.

Reagen & Hamonic in 1956 described cytologic differences between carcinoma Insitu and a group of less anaplastic lesions for which they introduced the term dysplasia.

If only the basal one third of epithelium characterized by cytologic atypia, increased mitotic activity and loss of polarity - they were referred to as mild dysplasia. If changes extending into the middle third - moderate dysplasia and more than 2/3rd of epithelium involved severe dysplasia. International congress on exfoliative cytology in 1961 accepted the following definition.

The original cytologic classification (Class System) of papanicolaou was replaced gradually by histologic terms of mild, moderate, severe dysplasia and carcinoma in situ and then came the Bethesda system in 1989 which combined HPV cytopathologic effects, often referred to as koilocytosis with mild dysplasia or CIN I to LSIL (Low grade squamous intraepithelial lesion) and moderate, severe, CIS ad HSIL (High grade squamous intraepithelial lesion) and today the Bethesda 2001 classification have been widely used.

Bethesda System

<table>
<tr><td>WNL</td><td>ASC-US</td><td>LSIL</td><td>HSIL</td><td>HSIL</td><td>Carcinoma</td></tr>
<tr><td colspan="6">Dysplasia / CIN System</td></tr>
<tr><td rowspan="2">Normal</td><td>Inflam</td><td>Mild dysplasia CIN 1</td><td rowspan="2">Moderate dysplasia CIN 2</td><td>Severe dysplasia</td><td>CIS</td><td rowspan="2">Cancer</td></tr>
<tr><td>Atypia</td><td>Koilocytosis</td><td colspan="2">CIN 3</td></tr>
<tr><td colspan="6">Old Pap System</td></tr>
<tr><td>Class I</td><td>Class II</td><td>Class III</td><td>Class III</td><td colspan="2">Class IV</td><td>Class V</td></tr>
</table>

In 1975 **WHO** defined dysplasia as a lesion in which part of the epithelium is replaced by cells showing varying degrees of atypia.

Richart grades them according to number of parabasal cells.

Less than 10% Parabasal cells	-	mild dysplasia
10 – 20%	-	moderate dysplasia
>30%	-	severe dysplasia

Reagen grades them according to nuclear size

		Average nucleus size
study of 2500 normal cells	-	7 microns
study of 5000 dysplastic cells	-	14 microns
study of 6500 CIS cells	-	13 microns

SCREENING FOR CERVICAL NEOPLASIA

In 1928 **Dr. George N. Papanicolaou,** an anatomist reported that malignant cells from the cervix could be identified in vaginal smears in his report on **"new cancer diagnosis".**

A Canadian gynaecologist **Dr. J. Ernest Ayre** 1947 suggested taking samples directly from the cervix with a wooden spatula rather than from the vagina with a pipette as Originally described by **papanicolaou**.

The first screening clinics were established in 1940's.

Recommended screening interval vary among different countries.

When to start

The American Cancer Society recommends that all women who are or have been sexually active or are 18 yrs. of age or older whichever is earlier have an annual pap test and pelvic examination.

Canadian Task Force 1982 also suggests this.

What should the pap smear interval be

Ideally pap smear has to be repeated annually. But this may not be cost effective. The Canadian Task Force 1982 suggested that a pap smear at 3 yrs. interval would be adequate upto the age of 55 yrs. Thereafter the chances of developing cancer cervix is remote.

WHO advices that each women must undergo a cytology screening at least once in her life time. Case control studies on cervical cancer screening found a relative fall in incidence of 2.7% in Canada by **Clark** and **Anderson** and 3.2% in Switzerland **(Raymond et al 1984)** after one or more negative smears.

It may be worthwhile to keep the following recommendations of the United States preventive services task force (US PSTF) in mind while considering the above mentioned issues.

- All women who are sexually active should be offered screening.
- Screening should begin at 21 years of 3 years within starting sexual activity, whichever is earlier.
- Screening is recommended every 3 years.
- Screening is not recommended in women > 65 yrs provided they have been regularly screened before and are not at a high risk for cervical cancer.
- Current evidence is insufficient to recommend for or against the use of routine HPV testing for screening for cervical cancer.

Screening should take place at least every 3 years. Despite these globally positive results, errors do occur in using the pap smear.

What is the appropriate age to stop screening

The appropriate age to stop screening is still undefined but as more women enter properly structured programmes it is more likely that the age for discontinuation will fall rather than rise.

Efficacy of pap smear

Eventhough pap screening is most simple and economical method it is not 100% accurate and it is credited with 87% accuracy.

It has a certain false positive and false negative rate.

A single pap smear has a sensitivity of only 50-60% , this means that a single test will not detect a cervical lesion in many women. However even with this limited sensitivity if three consecutive tests are negative there is less than a 1% chance that the patient will have a cervical abnormality.

It has also been admitted that the method was ardous and time consuming in the microscopic search for the specifically malignant cells sometimes obscured by the cellular desquamate, leucocytes and blood. Since then efforts have been made to improve the technique, simplify the methods and extend its application.

A meta analysis consigning data from 59 studies compared pap with histology and concluded that pap is unable to achieve high sensitivity and high specificity concurrently. **(Fahey et al 1995)**

False Positive

Reasons

Atypical cells especially those shed from hyperplastic and metaplastic cervical lesions, acute inflamnation often assoicated with hypoestrogenesim resembles carcinomatous cells.

False Negative

Reasons

- Improper cell collections
- Absence of endocervical cells
- Smears too thick
- Bloody smears
- Improper fixation
- Incorrect staining

Liquid based Cytology

The introduction of cyto centrifuge in 1966 was a great step forward in LBC **(Watson 1966)** and it is a new way of preparing cervical samples for examination in the laboratory.

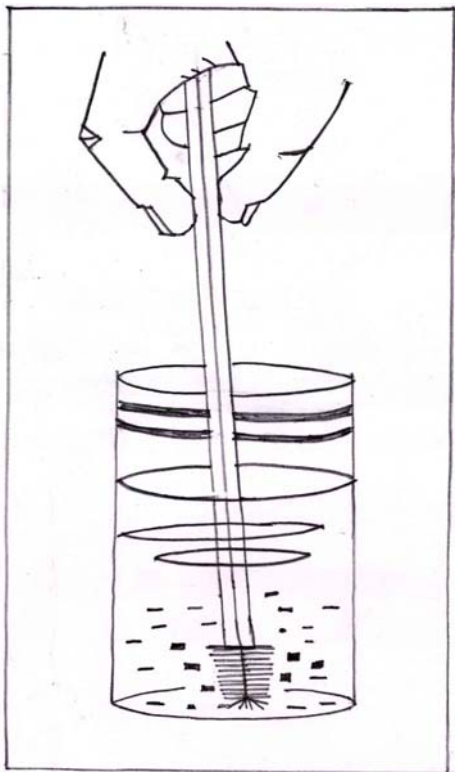
To decrease the false negative rate of cervical cytology over the past several years several liquid based techniques have been developed. These techniques differ from the conventional method of pap smear collection in several ways.

Once the scrapings are taken from the SCJ and transformation zone area the brush is rinsed directly into the vial containing preservative fluid, rather than being smeared on a glass slide. The vial is labelled and sent to the cytology laboratory.

Once in the lab, the sample fluid is spun and treated to remove obscuring material for example mucus or pus and a random sample of the remaining cells is

taken. The slide is then stained with the conventional papanicolaou stain and slide read under microscope.

Several studies have shown that more diagnostic cervical cells are collected by this liquid based technique and provide a cleaner appearance with less clumping, blood and inflammatory changes thus providing a better specimen and hopefully a better interpretation.



LBC reduces the rate of false -ve results from both screening and interpretation errors.

LBC has reduced the pressure on a skilled work force reduced money overall, reduced levels of anxiety in women, a quicker reporting time.

The evaluation of pilot studies and NICE recognises that LBC is as good as conventional smear test and it is cost effective.

Specimen Adequacy

One of the most important advances of the Bethesda system is its recommendation that each pap report should begin with a statement of adequacy. The 2001 Bethesda system has categorised the specimen adequacy as follows :-

Satisfactory for evaluation indicates the presence of

- A satisfactory squamous component.
- Adequate endocervical / transformation zone component.
- Obscuring elements (inflammation, blood, drying artifact, other) may be mentioned if 50-75% of epithelial cells are obscured.
- Relevant clinical information
- Appropriate labelling and indentifying information

Satisfactory for evaluation but limited by

- Lack of patient clinical information
- Partially obscuring blood, inflammation with precludes interpretation of approximately 50-75% of the epithelial cells.

Unsatisfactory for evaluation

Specimen rejected/not processed Reasons may include :

- Lack of patient identification
- Unacceptable specimen (eg. Slide broken beyond repair)
- Insufficient squamous component
- Obscuring elements cover more than 75% of epithelial cells.

One of the components of adequate smear is an adequate squamous component. According to Betnesda the requirement for an adequate squamous component was defined as well preserved and well visualized. Squamous epithelial cells should cover more than 10% of slide surface. The estimated minimum number of squamous cells for

Liquid based cytology – 5000

Conventional pap – 8000- 12,000

Because liquid based preparations likely represent a more homogeneous representation of the material obtained by the collection device a more stringent requirement was imposed on conventional smears.

A smear without endocervical cells is not considered unsatisfactory, although the absence of an endocervical / transformation Zone component is mentioned as a quality indicator.

New Diagnostic Screening Tests

Automated Screening Technology

The following technics that rely largely on neural network technology and are based on the computerized imaging and identification of abnormal cervical cells are available.

- Auto pap 300 (Tripath imaging, Burlington NC)
- PAPNET (Neuromedical systems).

Colposcope

Colposcopy is the examination of vagina and cervix with a binocular microscope. The word **"Colposcope"** is derived from the greek word kolpos (fold or hollow) and skope (examine).

The first colposcope was developed by **Hans Hinselmann** of Hamburg, Germany in 1925. Colposcopy has become an integral part of modern Gynecologic practice. It is extensively used for the evaluation of epithelium of cervix although the other indications for colposcope has increased.

Colposcopy is best performed in concert with cytology.

Colposcopic examination

The are two methods of examination.

1. The saline method
2. The classical or extended method.

The classical or extended method is widely used.

Indications for colposcope

1. Abnormal pap smears
2. Colposcope directed Biopsy in patients with abnormal pap smear.
3. VIA positive sites for biopsy
4. Suspicious cervix

Grading

The grading system devised by **coppleson and co-workers** is extensively used in modern colposcopy.

Grade I (insignificant, not suspicious)

Acetowhite epithelium, borders not necessarily sharp, absence of atypical vessels.

The predicted histology is CINI (LSIL), metaplastic epithelium (mature and immature).

Grade II (Significant, Suspicious)

Acetowhite epithelium with sharp borders, regularly shaped vessels, absence of atypical vessels.

The predicted histology is CIN 2- 3 (HSIL)

Grade III (Highly significant, highly suspicious)

White or grey opaque epithelium, sharply bordered; irregularly shaped atypical vessels predicted histology CIN 3 (HSIL) or early invasive cancer.

Benefits of Colposcope

- This can be done on outpatient basis.
- A directed biopsy for definitive histological diagnosis could be performed if required, then and there.
- If required the pre-cancer lesion could be treated with cryotherapy immediately.
- The future management could be planned without delay.

Basis of Colposcopic Appearances

International Federation of Cervical Pathology and coloposcopy May 1990, Italy).

A. Normal Colposcopical findings:

- Original Squamous Epithelium
- Original Columnar epithelium
- Transformation Zone (Metaplastic epthelium)

B. Abnormal Colposcopic findings:5

Within the transformation zone

1. Acetowhite Epithelium
2. Leukoplakia (thin or Thick)
3. Mosaics (fine or coarse)
4. Punctation (fine or coarse)

5. Atypical vessels

Histopathological Examination

Histopathological examination is generally regarded as the gold standard in the diagnosis of cervical carcinoma so that the **conventional teaching is that a positive cytology must be confirmed by Biopsy**. However reports of false positive and false negative do exist. Studying concordance and discordance between histopathology, cytology and colposcopic diagnosis of colposcopically directed biopsy make screening easier and more sensitive.

Correlation between cytology report and Histopathology report

Advantages

Cytopathological methods provide a rapid, inexpensive simple means of diagnosis.

1. No injury to tissue is produced
2. Psychological advantages, better accepted by the patient and the physician because it is often considered to be a routine test.
3. Covers a wider surface than that involved in a biopsy.
4. Cells can be obtained from areas inaccessible to a biopsy.
5. Smears permit a better evaluation of the nature of inflammation or infections.

Limitations

1. The cytologic diagnosis is not always final, it must be confirmed by histology.

MATERIAL AND METHOD

Selection of Cases

A random selection of 300 patients attending as outpatient in gynaecological department at government Kilpauk Hospital, chennai during the year 2005- 2006 .

Inclusion Criteria

Women who are sexually active, including post menopausal women. No previous screening test taken .

Exclusion Criteria

Antenatal and Postnatal mothers, previous screening test taken, proven preinvasive lesions and on treatment, menstruating women.

Method

A detailed history of the patient taken and the patient informed about the screening procedures and counselling given regarding the necessity for their participation in screening program.

Their awareness regarding the screening Programs and tests offered were assessed. Both conventional pap and liquid based cytology were performed in the same patient.

Pap smear

Materials

Cusco's bivalved self retaining speculum

Nulliparous - 28mm

Postmenopause - 28mm

Multiparous - 36mm

Light source

Ayre's Spatula

Glass slide

Marker pencil

Sterile glove

Cytofix spray

Method

Patient was put in lithotomy position and a suitable size cusco's speculum was introduced without lubricant. Cervical smear taken with Ayre's spaula rotating it through 360° over the squamocolumnar junction.

The smear was evenly spread over the glass slide marked with the pap smear number for that patient and immediately spray fixed.

Liquid based cytology

Materials

Cusco's bivalved self retaining speculum

Light source

Cervical brush

Vial with 6ml of methanol based preservative solution

Sterile glove

After conventional pap taken the cervical brush is inserted into cervical canal, some bristles should still be visible. If inserted too far there may be inadvertent sampling of the lower uterine segment (LUS) which causes diagnostic difficulties because its epithelium resembles HSIL, and adenocarcinoma insitu (AIS). Brush is used to take both ecto / endocervical sampling. Brush is rotated in the canal 180 degrees to limit bleeding and to increase specimen adequacy.

A full rotation is unnecessary because the circumferential bristles are in contact with the entire surface the moment the brush is inserted.

The brush is immediately rinsed in to 6 ml of vial containing preservative fluid and capped.

The slide and the vial are labelled and sent to the laboratory. The conventional smear containing slide is stained directly by the papanicolaou staining method.

Lab processing

The vial sample is now transferred to the cell funnel (reusable) and funnel is attached to a single circle slide with a filter card in between. The filter card will have a small hole for collection of cells on to the slide. The circle on the slide and filter card hole should be at the same side. The cell funnel, filter card and slide are attached together in a cell clip and placed in a aerosol tight sealed cell spin rotor which is designed for upto 12 samples x 6 cc per run. This cell spin rotor is placed in cytospin.

Cytospin is a cytocentrifuge which concentrates only cells in the liquid sample on to the slide. The supernatant fluid containing no cells and obscuring material like blood and mucus is absorbed by the filter card. The cytopsin is operated and cell spin rotor is subjected to 3,000 rpm for 10 minutes the slide with the resulting cell sample is now taken from the cell clip and stained by routine papanicolaou stain. Patients who were found to be with abnormal cytology reportes were subjected to colposcopy directed biopsy.

Cell Staining

Consistency and reliability in staining are the corner stones of cytological interpretation. The universal stain for cytological preparation is papanicolaou stain.

Harris haematoxylin is the optimum nuclear stain and the combination of 0G6 and EA 50 give the subtle range of green, blue and pink hues to the cell cytoplasm.

Staining Method

The slides are stained by the following procedure

1. Remove polyethylene glycol fixative in 50% alcohol 2 min. This step is important in preparation of spray fixed sample that is to remove carbowax. Without this important step the dye will not be able to penetrate the cells, resulting in cloudy or hazy appearance, especially of nuclear chromatin pattern.
2. Hydrate in 95% alcohol 2 min and 70% alcohol 2 min
3. Rinse in water 1 min.
4. Stain in Harri's Haemotoxylin 5 min.
5. Rinse in water 2 min.
6. Differentiate in 0.5% aqueous hydrochloric acid 10 seconds approx.
7. Rinse in water, 2 min.
8. 0.1% of ammoniated water, 2 min.
9. Rinse in water, 2 min.
10. Dehydrate, 70% alcohol for 2 min.
11. Dehydrate, 95% alcohol for 2 min.
12. Dehydrate, 95% alcohol for 2 min.
13. Stain in 096, 2 min.
14. Rinse in 95% alcohol, 2 min.
15. Rinse in 95% alcohol, 2 min.
16. Stain in EA 50, 3 min.
17. Rinse in 95% alcohol, 1 min.

Slides are mounted on with DPX.

Microscopic appearance

Nucleus	-	Blue colour
Cytoplasm of superficial Cells	-	Pink
Intermediate cell	-	Bluish Green
Cytoplasm (non –keratinizing squamous cells)	-	blue / green
Keratinizing cells	-	pink / orange

Abnormalites noted

Disproportionate nuclear enlargement

Variation in size and shape of nuclei

Irregularity of nuclei outline

Hyper chromasia and clumping of nuclear chromatin

Abnormal no. of size or form of nucleoli

Multi nucleation associated with any of the above.

Perinuclear halo.

Colposcopy

Materials

Colposcope

Bivalved cusco speculum

Cotton tipped swabs

Sterile glove

Normal saline

3% Acetic acid

Lugol's Iodine

Examination table with height adjustment.

The magnification is 13.5 times.

With the patients in lithotomy position colposcope was positioned and the objective lens adjusted to bring the cervix into focus.

The cervix and vagina are cleaned with cotton swab with normal saline cervix was inspected for lesions leucoplakia, carcinoma, viral condylomata. Then a solution of 3% acetic acid was liberally applied over the cervix. The solution is mucolytic and changes the colour and vascular pattern after an internal of 10 - 30 seconds.

The cervix was inspected for colour, surface, columnar epithelium, transformation zone, SCJ and vascular pattern. The vascular pattern was again studied using a green filter schiller's Iodine test was done for patients with suspicious lesions.

The special symbols for the different colposcopical patterns are used by the colposcopist to document the colposcopic finding which imitate as closely as possible the picture observe in the colposcope.

The 2 recording systems in vogue are

1. **Odell diagram** colposcopic lesions may be represented in a circular diagram in relation to the os.

2. Modified Hammond's graph of cervix.

It consists of 3 concentric circles with 12 radial lesions in clockwise fashion. The inner most represent endocervix, intermediate one is the transformation zone and the outermost is the ectocervix..

Biopsy cervix

Materials

Sterile glove

Vulsellum

Light source

Tischler biopsy forceps

Container with 10% formalin

The biopsy material was fixed in 10% formalin immediately. The fixed material was then imbedded in wax for section cutting. The sections were then subjected to Haemotoxylin and eosin staining for reading the changes in the squamous lining in respect of inflammation, ulceration, dysplasia, CIS, micro invasive carcinoma and invasive carcinoma.

The management of abnormal lesion is finally dependent upon the histopathological diagnosis. Biopsies were taken from Iodine negative areas or

areas of atypical colposcopic findings. all biopsies were done under colposcopic guidance.

RESULT AND ANALYSIS

TABLE - 1

AGE DISTRIBUTION OF THE PATIENTS WHO WERE SCREENED WITH CYTOLOGY

Age in decades	Number of cases	Percentage
20-30	78	26
31-40	151	50.3
41-50	65	21.7
51-60	6	2
Total	**300**	**100**

Mean ± S.D = 35.73667 ± 7.219491

The number of cases screened were more in the age group of 31 - 40 - 50.3%.

TABLE - 2

PARITY DISTRIBUTION

Parity	Number of cases	Percentage
0-2	117	39

3-5	180	60
>5	3	1
Total	**300**	**100**

61% of the cases screened were multipara $\geq$ 3

TABLE - 3

EDUCATIONAL STATUS

Education	Number of cases	Percentage
Illiterate	114	38
Primary	68	22.7
Secondary & Above	118	39.3
Total	**300**	**100**

TABLE - 4

SOCIOECONOMIC STATUS

Class	Number of cases	Percentage
I	-	-
II	-	-
III	45	15
IV	120	40
V	135	45
Total	**300**	**100**

TABLE - 5

MENSTRUAL STATUS

	No.of cases	Percentage
Menstruating	291	97
Post menopausal	9	3
Total	**300**	**100**

TABLE - 6

	Mean ± SD
Age at 1st coitus	18.87 ± 2.47476
Age at Marriage	18.93 ± 2.501859
Duration of Marriage	16.20 ± 7.831671
LCB	8.11 ± 4.779877

This table shows early age of marriage and 1st coitus among the study group.

TABLE - 7

CONTRACEPTION

	Number of cases	**Percentage**
Barrier (condom)	3	1
IUCD	9	3
OCP	6	2
Female sterilization	144	48
Male sterilization	-	-
No method followed	138	46
Total	**300**	**100**

99% of cases in this study has constant sperm exposure. Only 1% followed barrier contraception.

TABLE - 8

ABORTION STATUS

	Number of cases	**Percentage**
MTP with sterilization	27	9
Spontaneous abortion	51	17
MTP	12	4
No H/o Abortion	210	70
Total	**300**	**100**

9% of the cases screened had unwanted pregnancy and went for MTP with sterilization.

TABLE - 9

EXTRA / PREMARITAL CONTACT OF WOMEN

	Number of cases	Percentage
Yes	8	2.7
No	292	97.3
Total	**300**	**100**

TABLE - 10

EXTRA / PREMARITAL CONTACT OF HUSBAND

	Number of cases	Percentage
Yes	32	10.7
No	268	89.3
Total	**300**	**100**

TABLE - 11

TREATED FOR STD

	Number of couples	**Percentage**
Yes	48	16
No	252	84
Total	**300**	**100**

16% of cases screened have taken treatment for STD including partner treatment.

TABLE - 12

CERVICAL CHANGES IN WOMEN TREATED FOR STD

LBC	**Treated for STD (n=48)**	
	No.of cases	**Percentage**
Normal	35	72.9
Cervical changes	13	27.1
Total	**48**	**100**

Out of 48 couples treated for STD 13 women had cervical changes. This shows the impact of sexually transmitted disease in the etiology of cancer cervix.

TABLE - 13

PRESENTING COMPLAINT

Complaints	Number of cases	Percentage
White discharge	173	57.7
UTI	34	11.3
Lower Abdominal pain	34	11.3
Low Back Ache	30	10
Inferility	4	1.3
Mass P/V	11	3.7
Mass P/A	4	1.3
Dysmenorrhea	10	3.4
Total	**300**	**100**

57.7% of cases screened has their main complaint as white discharge PV. The next common complaint was urinary tract infection and Lower abdominal pain.

TABLE - 14

CERVICAL STATUS

	Number of cases	Percentage
Normal	100	33.3
Erosion	140	46.7
Hypertrophy	35	11.7
Old cervical tear	25	8.3
Total	**300**	**100**

46.7% of cases screened had cervical erosion and 33.3% had normal cervix with speculum examination.

TABLE - 15

LOCAL EXAMINATION

	Number of cases	**Percentage**
Normal	211	70.4
Discharge	56	18.6
UV prolapse	9	3
Excoriation	12	4
Wart	7	2.3
Others	5	1.7
Total	**300**	**100**

About 70.4% cases screened were normal in local examination. 18.6% of cases had discharge.

TABLE - 16

INFECTIONS

	Number of cases	**Percentage**
Normal	240	80
Trichomonas	40	13.3
Candida	20	6.7
Total	**300**	**100**

13.3% of cases screened had Trichomonas infection and 6.7% of cases screened had candidal infection. Out of 6.7% cases 2% cases were known diabetic and on treatment.

TABLE - 17

CYTOLOGIC DIAGNOSIS

Cytology	Pap		LBC	
	n	%	n	%
Normal	64	21.3	232	77.3
Inflammatory smear	200	66.7	16	5.3
Mild dysplasia	30	10	32	10.7
Moderate dysplasia	3	1	3	1
Severe dysplasia	2	0.7	11	3.7
Cancer	1	0.3	6	2
Total	**300**	**100**	**300**	**100**

LBC - LSIL - 10.7%, HSIL - 4.7%, Cancer - 2%

PAP - LSIL - 10%, HSIL - 1.7%, Cancer - 0.3%

TABLE - 18

COST ESTIMATION PER WOMAN

Materials	Pap (Rs.)	LBC (Rs.)
Ayre's Spatula	6	-
Brush	-	12
Slide	1	1
Cytofix spray	3.50	-
Vial with preservative fluid	-	16
Lab processing	23	40

Total	**33.50**	**69**

TABLE - 19

COMPARISON OF SPECIMEN ADEQUACY OF LBC WITH THAT OF CONVENTIONAL PAP

		PAP		LBC	
		n	**%**	**n**	**%**
1.	**Satisfactory**	170	56.7	290	96.7
2.	**Satisfactory for evaluation but limited by**				
	(a) Air drying artifact	39	13	1	0.3
	(b) Thick smear	37	12.3	4	1.3
	(c) Endocervical component absent	14	4.7	2	0.7
	(d) Scant squamous epithelial component	12	3.3	2.	0.7
	(e) Obscuring blood	24	8	1	0.3
	(f) No clinical history	-	-	-	-
	(g) Cytolysis	2	0.7	-	-
	(h) Others	2	0.7	-	-
3.	**Unsatisfactory for evaluation**				
	(a) Air drying artifact	-	-	-	-
	(b) Thick smear	-	-	-	-
	(c) Endocervical component absent	-	-	-	-
	(d) Scant squamous epithelial component	-	-	-	-
	(e) Obscuring blood	-	-	-	-
	(f) No clinical history	-	-	-	-
	(g) Cytolysis	-	-	-	-
	(h) Others	-	-	-	-

* A slide may have more than one factor.

TABLE - 20

SENSITIVITY / SPECIFICITY OF PAP

LBC			
Pap	**Cancer cervix**	**Normal**	**Total**
Cancer cervix	20 (a)	16 (b)	**36**
Normal	32 (c)	232 (d)	**264**
Total	**52**	**248**	**300**

Sensitivity (a/a+c) = 20/52 = 0.38
(true positive)

38%

Specificity (d/b+d) = 232/248 = 0.93
(true negative)

93%

Positive predictive value (a/a+b) = 20/36 = 0.55

55%

Negative predictive value (d/c+d) = 232/264 = 0.87

87%

Percentage of false positive (b/b+d) = 16/232 = 0.069

6.9%

Percentage of false negative (c/a+c) = 32/52 = 0.61

61.6%

TABLE - 21

CERVICAL CHANGES DETECTED BY LBC WITH THAT OF HISTOLOGY

HISTOLOGY						
LBC	**Cervicitis**	**MD**	**MOD**	**SD**	**Ca**	**Total**
MD	12	19	1	-	-	32
MOD	-	1	1	1	-	3
SD	-	-	2	8	1	11
Ca	-	-	-	-	6	6
Total	**12**	**20**	**4**	**9**	**7**	**52**

Low grade squamous intraepithelial neoplasia (Mild dysplasia) - out of 32 cases 20 cases had cervical changes.

LSIL detection rate of LBC in this study is 63%.

High grade squamous intraepithelial neoplasia (Moderate and severe dysplasia) out of 14 HSIL 1 case was diagnosed as invasive cancer and 1 case as LSIL

HSIL detection rate 85%.

TABLE - 22

COMPARATIVE ANALYSIS WITH VARIOUS STUDIES

Authors	Sensitivity%		Specificity %	
	LBC	Pap	LBC	Pap
Sulik et al (2001)	70	79	85	89
Bergeron (2001)	66	61	9.6	11
Park (2001)	45	49	27	23
Bishop (1998)	89	78	44	17
Bolick (1998)	95	85	58	36
Ferris (2000)	52	63	99	99
Brown & Garber (1999)	93	82	96	96
Maxwell (2003)	67	60	97	97
Nice (2003)	67	60	97	97
Present study	97	38	56	93

TABLE - 23

VAGINAL CYTOLOGY REPORTS AT KMCH

FOR THE PAST 3 YEARS

Year	2003 (Pap)		2004 (Pap)		2005 (Pap)		Present study			
							Pap		LBC	
	n	%	n	%	n	%	n	%	n	%
Total slides	709	-	1540	-	890	-	300	-	300	-
Non Specific	252	36	476	31	285	32	64	21	232	77.3

Inflammatory	397	56	890	58	515	58	200	67	16	5.3
Atypical	60	8	174	11	90	10	36	12	52	17.4

TABLE - 24

SENSITIVITY / SPECIFICITY OF LBC

Histology			
LBC	**Cervical changes**	**Normal**	**Total**
Cervical changes	40 (a)	12 (b)	**52**
Normal	1 (c)	15 (d)	**16**
Total	**41**	**27**	**68**

Sensitivity (a/a+c) = 40/41 = 0.97
(true positive)

97%

Specificity (d/b+d) = 15/27 = 0.56
(true negative)

56%

Positive predictive value (a/a+b) = 40/52 = 0.77

77%

Negative predictive value (d/c+d) = 15/16 = 0.94

94%

Percentage of false positive b/b+d = 12/27 = 0.44

44%

Percentage of false negative c/a+c = 1/41 = 0.02

2%

TABLE - 25

SENSITIVITY / SPECIFICITY OF COLPOSCOPE

Histology			
Colpo	**Cervical changes**	**Normal**	**Total**
Cervical changes	33 (a)	8 (b)	**41**
Normal	8 (c)	19 (d)	**27**
Total	**41**	**27**	**68**

Sensitivity (a/a+c) = 33/41 = 0.8
(true positive)

80%

Specificity (d/b+d) = 19/27 = 0.7
(true negative)

70%

Positive predictive value (a/a+b) = 33/41 = 0.8

80%

Negative predictive value (d/c+d) = 19/27 = 0.7

70%

Percentage of false positive b/b+d = 8/27 = 0.3

30%

Percentage of false negative c/a+c = 8/41 = 0.2

20%

TABLE - 26

AGE DISTRIBUTION WITH PREINVASIVE AND INVASIVE LESIONS (HISTOLOGY)

Age	MD	MOD	SD	Ca	Total
20-30	7	2	-	-	9
31-40	8	2	4	3	17
41-50	6	-	5	4	15
>50	-	-	-	-	-
Total					**41**

The number of cases diagnosed histology as preinvasive and invasive lesions were more in the age group of 31 - 40 yrs (17%) followed by 41 - 50 yrs (15%)

TABLE - 27

COLPOSCOPY RESULTS

Grading	n=68	Percentage
Normal	27	40

I	15	22
II	19	28
III	7	10

DISCUSSION

The concept of screening has been defined as the search for unrecognized disease or defect by means of rapidly applied tests, examination or other procedures in apparently healthy individual.

The present study was conducted to evaluate the efficiency of liquid based cytology diagnostic modality in the diagnosis of cervical cancer and to quantitative its correlation with the histopathology.

In this study 300 patients were randomly selected and both conventional pap and liquid based cytology are applied to the same women and compared in a within subject analysis.

The advantage is that many characteristics are equivalent for both tests (including patient attributes, timing in the menstrual cycle, clinician factors). within subject analysis is common in diagnostic accuracy studies for cervical cancer screening because it is relatively simple to collect two samples during a pelvic examination.

- Of the total cases examined 50.3% cases were in the age group of 31 - 40 yrs.

- 61% of the cases screened were multiparous women.

- 38% of the cases were illiterate and 39.3% of cases had their secondary schooling and above.

- 45% of the cases screened were from socioeconomic class V and 97% of cases were menstruating.

- 99% of cases in this study followed other than barrier contraception, a main risk factor for cancer cervix in low socioeconomic group.

- 16% of couples had taken treatment for STD.

- The main complaint among the screened population was white discharge followed by urinary tract infection and lower abdominal pain.

Diagnostic accuracy

In this study LBC method of specimen preparation led to the cytological diagnosis of significantly more cervical abnormalities than the conventional method. (52 Vs 36).

Depending on the prevalence of the disease in a population there may be more cases of higher grade abnormalities such as high grade squamous intraepitralial lesion (HSIL) and cancer which are the most important outcomes for a test to detect.

LBC technique has detected more high grade lesions then that of pap (20 Vs 6%).

In one of the first studies done by **Wilbur** and associates a total of 3218 patients had a single cytologic sample that was split into matched pairs. The

inferred false -ve rate was 15% for cp and 4% for LBC. In this study false negative rate for CP is 61.6% and for LBC 2%.

The study by **Lee** there was 14% difference between the Cp & LBC.

Robert's and associates did split sample paired Cp & LBC in 35,560 patients and found LBC showed those severe abnormalities in 1194 cases compared with the Cp. In this study cases with severe abnormalities LBC 6.7% CP - 2%.

Bernstein et al., found that the overall sample adequacy improved with the LBC but the incidence and diagnosis of ASCUS was not reduced. The sensitivity of screening test was also found to be increased. The sensitivity of LBC in this study is 97%.

Infection

The detection of infections was very much increased in the LBC technique. Out of 40 Trichomonas infection detected 26 cases were detected with LBC. Out of 20 cases with candida LBC diagnosed 11 cases.

Specimen adequacy

Specimen adequacy also was improved significantly with the LBC method. The reduction in the number of slides compromised by obscuring amounts of blood, mucus, inflammation and air drying artifact may reduce significantly the need to repeat the screening procedure.

An increase is specimen adequacy is due to the fact that the cervical cells that are removed with brush are rinsed in a "direct to vial" method. All the cells are collected in the preservative solution immediately and also reduces the likelihood that a patient cell sample will be damaged by air, clumping etc and also the sample is subjected to a device where it is spun and the obscurring materials were absorbed by the filter card.

In case of pap the whole sample is not smeared on the slide and if there is a delay in fixation sample will be damaged by air drying artifact, clumping etc.

A 1994 study published in American Journal of clinical pathology found that upto 80% of a sample taken from a patient using the conventional pap smear techniques is not smeared on the slide but remains on the collection device.

Collection device

As the pap smear has been taken with a wooden spatula it is thought to reduce the sensitivity because of absorptive properties of wood.

In case of LBC brush is used which has showed a significant difference in the quality of the sample prepared.

There is evidence that the device used to collect cervical cell specimens plays a significant role in determining the sensitivity and specificity of the test (**Austin and Ramsey 1998).**

According to ASCCP guideline the increased sensitivity of the brush make it the preferred instrument for cervical sampling.

As spatula is used for pap sometimes scarring of the cervix, mucosal tears may happen and the blood is also collected on the slide make it different to read the slide.

The transformation zone as the age advances goes deeper into cervical canal for which brush will be a better option than that of spatula.

Cost effectiveness

Even though cost estimation per women in LBC is increased, the number of inflammatory smears detected in pap has been shown to be normal in LBC (66.7% Vs 5.3%).

This will reduce the treatment cost as well as the repeat smear cost after treatment for those with inflammatory smears.

Reduction in pressure on a skilled workforce as it is clearer to read samples and the workload and payment to the staff will be reduced.

The economic evidence of trial studies suggest that LBC screening every 3 years or longer after a normal test may be cost effective relative to pap smear screening every year.

As the number of prior normal LBC test increases the cost per life year saved will be increased substantially.

Table 22 - comparative analysis of various studies have shown the increased sensitivity of LBC over that of pap smear.

Vaginal cytology reports previous years show the inflammatory rate remains equal because of the direct smearing of the slide with sample so that blood, mucus, debris are transferred to the slide. Also cell over lapping and distortion due to air drying can complicate the evaluation of cell changes.

The smaller screening area on the microscope slide and the clarity of LBC specimen increase the ease of screening.

Results of LBC with that of histology

Detection of invasive or metastatic cancer is considered to be the gold standard a longitudinal study is best. Because of time, expense and difficulty involved with a longitudinal study an acceptable surrogate is histology. A clinical diagnosis is based on biopsy conformation.

The evaluation of women with negative test result is considered to be invasive and costly. As a result the use of colposcopy and the histological followup is limited to women with positive diagnosis identified by LBC and pap tests.

Out of 32 cases in LBC 19 cases where confirmed by histology as mild dysplasia; 12 cases as chronic cervicitis. 1 case in LBC was diagnosed as such as moderate dysplasia. Out of 6 cases 6 cases were diagnosed as invasive cancer.

HSIL - out of 14 cases 1 went as mild dysplasia (LSIL) and 1 as invasive cancer.

Duration of marriage had a strong impact on development of cancer cervix. The patients with severe dysplasia and cancer cervix has a longer duration of marriage (> 20 yrs) Those patients with normal cytology had a lesser duration of marriage < 10. yrs.

Treated for STD

Out of 48 coupes treated for STD 13 women had cervical changes in LBC. This shows the impact of STD in the etiology of cancer cervix.

Age distribution

The maximum indicence of cancer cervix is in the age group of 35 - 64 (ASRW 57.4) (MMTR Chennai, 2002).

In this study patients with HSIL were in the age group of 31 - 40 This shows the incidence of cancer cervix has shifted to a lower age group.

The average age of first coitus was 17 yrs for cases with cervical changes. This shows that early age of sexual activity has an strong impact.

Out of 2 post menopausal women with cervical changes one was diagnosed as severe dysplasia and another as mild dysplasia.

53% of cases with cervical changes belong to socioeconomic class V.

Extra / Premarital contact (women)

Out of 8 cases 1 case was diagnosed mild dysplasia 4 cases were normal 2 as severe dysplasia and 1 case as moderate dysplasia by histology.

Result of Colposcopy Vs histology

Out of 68 cases of colposcopy done 27 cases were normal of which 3 cases were diagnosed LSIL and 5 case as HSIL

Grade I (insignificant, not suspicious) - Total 15 cases 7 cases were LSIL.

Grade II (Significant suspicious) - Total 19 cases 11 cases were diagnosed as LSIL and 4 cases as HSIL and 4 cases as invasive cancer.

Grade III (highly significant, highly, suspicious) - Total 7 cases 4 cases as HSIL and 3 cases as cancer.

Distribution of colposcopic findings

1. Normal study - 27
2. Abnormal
   - Acetowhite epithelium - 12
   - Punctation - 6
   - Mosaic - 3
   - Leucoplakia - 2
   - Atypical vessels - 3
3. Frank invasive carcinoma - 7
4. Erosion - 8

The diagnostic accuracy of CIN detected by colposcopy given by various authors.

SCOH	1967	90%
S.S.Iyar	1979	87%
Bandi et al	1985	89%
Usha Surayi	1986	92.6%
Present study		80%

The frequency of cancer detection by colposcopy by various authors and present series.

Zurich	-	2.8%
Limburg	-	9.8%
Brentran	-	11.3%
Burgart	-	10.08%
Present series	-	10.3%

SUMMARY

Out of 300 patients screened for cancer cervix with conventional pap and Liquid based cytology in the same patient

a. LBC detection rate of cervical abnormalities and HSIL was more than that of CP.

b. False -ve rate of LBC only 2%

c. Sensitivity 97% and false positive rate is 44%

d. The sensitivity is as equal to gold standard method.

e. Infection detection rate increased with LBC

f. Specimen adequacy improved with LBC substantially

g. The collection sample device brush found superior to wooden Ayre's spatula both not in injuring tissues and specimen collection.

h. The adverse impact on a women's quality of life caused by unnecessary repeat smears and possible investigations would reduce the cost with LBC.

i. The economic evidence suggests that LBC screening every 3 yrs of longer may be cost effective.

j. LBC reduced the pressure on a skilled workforce.

Colposcopy has become as integral part of modern gynaecologic practice. the sensitivity and specificity is high. However its main indication remains examination of women with abnormal smears and a trained personnel is required as false positive results may end up in unnecessary treatment modalities and only ecto cervix lesions can be detected.

As cytology is ideal for mass screening, specimen can be obtained by non medical professional, detects lesion both in ecto and endo cervix and cost effective LBC is a better alternative and colposcopy directed biopsy can be done in patients with abnormal smears.

Scope for future study

LBC have been developed to improve the detection of cervical cancer and its precursors and reduce the rate of false negative results from conventional cervical smear tests. In several countries liquid based cytology is replacing conventional smear tests. A thorough economical evaluation is needed for this new technique (LBC) to be implemented in our country as a mass screening and also human papilloma virus testing as complementarily to conventional smear testing should be further evaluated in clinical research.

As thin prep and surepath method of thin layer preparation is automatic and costlier an alternative and cheaper method of cytocentrifuge is suitable for our country. The cost effectiveness and accuracy can be done in a large scale trial.

CONCLUSION

WHO Press Release, 11 October 2001, points out that.

We should aim to divert out resources for screening and treating the high risks group of women. The effort once or twice in their lifetime will reduce the incidence of cervical cancer by 50%.

In this scenario mass screening with LBC which has a high detection rate for HSIL and colposcope for abnormal smears offers a potent method of rapid assessment of any dysplasia possibly present.

LIST OF ABBREVIATIONS

CIN	-	Cervical Intraepithelial Neoplasia
CIS	-	Carcinoma in situ
WHO	-	World Health Organization
ICMR	-	Indian Council of Medical Research
HPV	-	Human Papilloma Virus
HSV	-	Herpes Simplex Virus
OCP	-	Oral contraceptive pill
HLA	-	Human Leukocyte antigen
STD	-	Sexually transmitted Disease
DNA	-	Deoxy ribo nucleic acid
IARC	-	International Agency for research in cancer
MHC	-	Major Histocompatability complex
HIV	-	Human immunodeficiency virus
LBC	-	Liquid based cytology
PAP	-	Papanicoloau
LSIL	-	Low grade squamous intraepithelial lesion
HSIL	-	High grade squamous intraepithelial lesion
SCJ	-	Squamous columnar junction
NICE	-	National Institute for clinical excellence
CP	-	Conventional Pap
-ve	-	Negative
+ve	-	Positive
ASCUS	-	Atypical squamous cells of undetermined significance
HCII	-	Hybrid culture II assays
LAMS	-	Latin American Screening

ASCCP - American society for colposcopy and cervical pathology

PROFORMA

Name

Age

Sl. No.

OP No.

SE Status

Residence

Menstrual History

Married **Yes / No**

Age at Marriage

Sexual History

Husband : **Premarital**
Extramarital

Patient : **Premarital**
Extramarital

Obstetric History

Contraceptive methods

Presenting Complaint

a) White discharge duration
b) Post coital bleeding
c) LAP

d) Backache
e) Post Menopausal bleeding

Past Medical History

a) Treated for STD

General Examination

Per Abdomen

Per Speculum

Per Vagimum

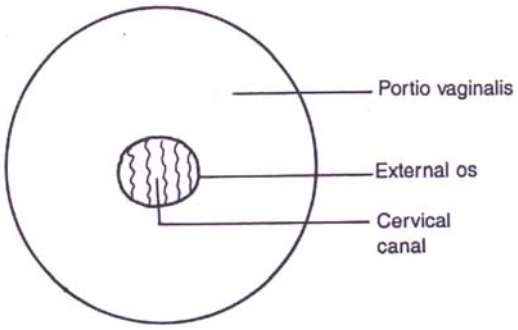
Per Rectum mucosa free Yes / No

Diagnosis

PAP

LBC

COLPOSCOPY



Odell's Diagram

Histopathology report

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